Journal of Pharmaceutical Chemistry
http://www.vensel.org/index.php/jphchem
VENSEL

Antitubercular drugs: advances in nitrogen containing heterocyclic compounds and some other derivatives

[1,*]Mohammad Asif

[1]Department of Pharmacy, GRD (PG) Institute of Management and Technology, Dehradun (Uttarakhand), 248009, India

Abstract: Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is an infectious disease. Control of TB is complicated by difficulties in the long-course chemotherapy treatment, the inability to eliminate latent microbes, and the increasing emergence of Multidrug Resistant (MDR) strains of *M. tuberculosis*. New anti-TB drugs are urgently needed, including developments of short-term treatments to minimize the emergence of drug resistance and new drugs to treat multidrug resistant tuberculosis and to eliminate the latent microbes. Many new structural anti-TB agents exhibited promising activities against susceptible and resistant strains of *M. tuberculosis*. The diarylquinoline with superior anti-tuberculotic activity and encouraging results of nitroimidazopyrans and oxazolidinones have generated considerable excitement.

Keywords: Tuberculosis, drug resistance, drug development, mycobacterial cell wall.

1. Introduction

*Mycobacterium tuberculosis*is, a causative agent of tuberculosis (TB), has latently infected one third of the world population. The infection is caused via inhalation of few droplets containing *M. tuberculosis* bacilli.[1-3] After infection, *M. tuberculosis* pathogenesis takes place in two stages.

- an asymptomatic state that can persist for many years in the host, called latent TB.
- The second stage requires only a weakened immune response to become activated (Zhang, 2004),[4] then the bacteria begins replicating and causing typical symptoms such as cough, chest pain, fatigue and unexplained weight loss. If left untreated, the disease eventually culminates in death.

The appearance of Human Immunodeficiency Virus (HIV) and the Acquired Immune Deficiency Syndrome (AIDS) epidemic emphasized the significance of reactivation of the disease. Over 50% of deaths among HIV-infected patient results from co-infection with *M. tuberculosis* with the two pathogens inducing each other's replication, thus accelerate the collapse of the immune system. The World Health Organization (WHO) report estimates that close to 2 million deaths occur every year, that there are around 8 million new cases per annum, and that every third person on the earth has been exposed to or infected by *M. tuberculosis*.[5, 6] Even though TB can be treated and even cured with chemotherapy, treatment is lengthy and takes 6-9 months.[7] In addition to lengthy therapy, significant toxicity and poor patient compliance, drug resistant and multidrug resistant TB (MDR-TB) poses a greater challenge in controlling TB.[1-3]

Currently, TB chemotherapy is made up of first-line drugs, Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB), which are given for six months. If this treatment fails due to bacterial drug resistance or intolerance to one or more drugs, second-line drugs; *para*-aminosalicilate (PAS), Kanamycin, Fluoroquinolones, Capreomycin, Ethionamide and Cycloserine are used. These are generally less effective or more toxic with severe side effects.[7-9] This second-line treatment can also be ineffective since MDR-strains exhibit resistance to most of second-line drugs.[10] Treatment is also quite difficult by the presence of metabolically silent, persistent or dormant tubercular bacteria within host lesions. These are not susceptible to the anti-TB drugs that usually kill growing but not persistent bacteria.[4] There are so many reasons for drug resistance, including prescription of inadequate regimens, an uncertain drug supply, ineffective drugs, duration of lengthy treatments which is one of the major contributors because some TB patients prematurely stop their therapy after an initial, rapid health improvement, thereby favoring the appearance of drug-resistant strains.[11]

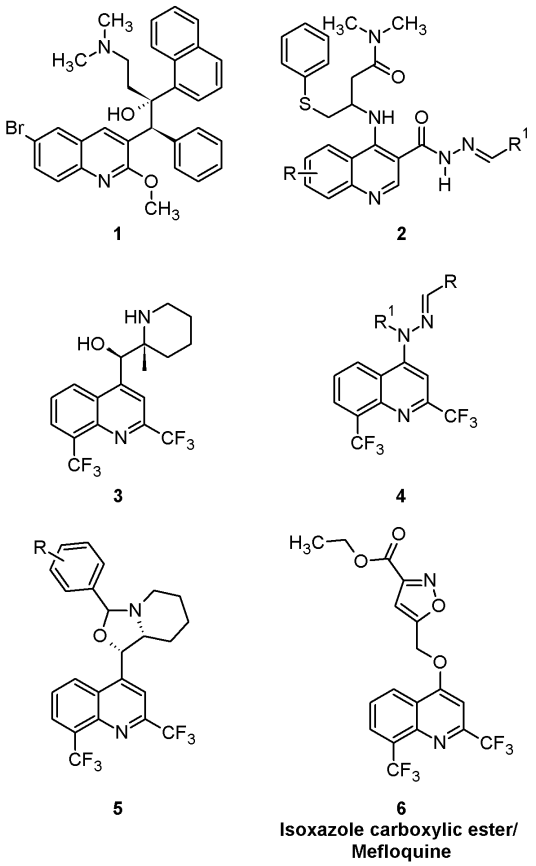
2. Rational drug design: In new pharmacophore groups, one problem that must be considered in the design of anti-TB compounds is that there is a subpopulation of bacteria in a persistent non-replicating state. This is considered a major contributing factor to long drug treatments for TB.[12] For this reason, it is important to determine if compounds have potential activity against these bacteria at the onset of design. The physicochemical properties were also studied that directly affect the pharmacokinetics and pharmacodynamics of drugs. It is the influence of

Submitted on: Apr 15, 2014
Revised on: Jul 01, 2014
Accepted on: Jul 09, 2014
*corresponding author: AM; E-mail: aasif321@gmail.com

stereoisomers on biological activity, because individual enantiomers have significant differences in activity, although sometimes the activity of some enantiomers cannot be explained.

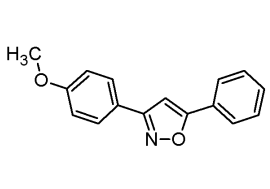
3. Non-fluoroquinolones

A quinoline ring is one of the moieties frequently used in drug design and development. It has been a privileged pharmacophore for the design of anti-TB agents. Diarilquinoline, TMC207 (**1**), is an ATP synthase inhibitor is one of the most important non-fluorinated quinolone compounds with potential anti-TB activity. Butanamide and carbohydrazone moieties are the two well-established pharmacophore with good antibacterial activity. The design of new quinoline derivatives with active carbohydrazine and butanamide moieties in 3rd and 4th position, respectively, has been carried out. These compounds shows that the presence of a trifluoromethyl group at 8th position increases activity; however, the fluoro group in 6th position partially decreases activity (**2)** and these type of compounds were relatively less toxic.[13] The development of mefloquine analogs (**3**) in a series of compounds (**4**), good anti-TB activity has been recognized in molecules with heterocyclic groups like pyrazole, imidazole, and indole rings on the quinolone moiety. Compounds with a pyrazole ring have shown activity against resistant strains that can be accredited to the presence of electron donating groups stabilizing the pyrazole ring, making it most active entity within this series.[14] A series of compounds with the conformationally restricted piperidinyl ring of mefloquine through the construction of an aryloxazolidine ring (**5**) has been reported with improved anti-TB activity. The activity of these compounds is influenced by substituents on the aromatic ring bound to C-17 of the oxazolidenyl nucleus. Compounds with electron donors (hydroxyl or methoxyl groups) capable of forming strong hydrogen bonds, were found to be active. While, compounds electron withdrawing (nitro or halogens) groups capable of forming only weak hydrogen bonds were inactive.[15] Design of mefloquine derivatives as anti-TB agents includes introduction of a hydrazone linker at 4-position of mefloquine, substitution of a piperidine with a piperazine ring and extension of the basic terminus of the piperazine ring at 4-position. While, Isoxazole fragments have been identified as one of the most promising hits in high-throughput screening against TB. Both types of compounds exhibit an aromatic ring, a two-atom linker and a five or six membered ring. Applying hybridization strategies a series of new chemical compounds (**6**) were reported with potential anti-TB activity. One major problem that has been reported with this class of compounds was their poor penetration, especially with acid derivatives, through the *M. tuberculosis* cell wall. While ester of these compounds may act as prodrugs as they tend to release their parent acid derivative (**6**) inside the pathogen. Structure activity relationship revealed that 2,8-ditriflurometh yl groups are essential for activity and attempts to replace it with methyl groups reduced its activity to 10-fold. Similarly, attempts to replace ester with its bioisosteres (amides, oxadiazoles) lead to the reduction in activity. Both electronic and steric factors of substitutions play a major role in determining the anti-TB activity of these compounds.[16]

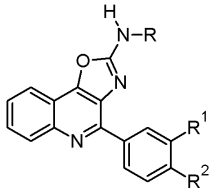


Isoxazole derivatives have been reported as anti-TB agents, for example, compound (**7)** with an activity of 2.9 μM, which is comparable to INH and RIF.[17] Thus, quinoline and oxazole ring hybridization were used to develop a series of new anti-TB agents (**8**), which have shown good activity due to presence of aryl substituents at 2nd position on quinoline ring. The introduction of a 1,3-oxazole ring significantly increases activity making them more potent than INH.[13] New moiety that confers anti-TB activity with low cytotoxicity, methoxybenzofuro[2,3-b]-quinoline derivatives (**9**), that have a potent *M. tuberculosis* growth inhibition of 99% at sub-micromolar (0.20μg/mL) concentrations with 50% inhibitory concentration at (IC_{50}) > 30.00μg/mL.[18] Several studies have investigated modifications in the quinolone ring, mainly at 3rd, 6th and 7th position. They made a modification in the 2nd position, including an aliphatic side chain with various degrees of unsaturation, chain lengths, and variation in position of double bond (**10**). The results showed that increasing the chain length enhances anti-TB activity, showing optimal activity with 14 C-atoms. If there is an increase of more carbon atoms in the chain, activity decreases dramatically. This behavior has also been described for ciprofloxacin derivatives where lipophilicity could play an important role in anti-TB activity. The saturated aliphatic chain has less activity than unsaturated analogues. The unsaturation of an aliphatic chain is an essential structure for anti-TB activity.[19]

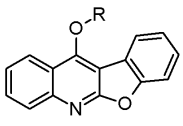
Phenazine and quinoxaline rings are considered bioisosteres of the quinoline ring. Phenazine derivatives are useful compounds for new anti-TB drug development, particularly Tubermicyn B and Clofazimine (phenazine analouges). Similarly, a series of



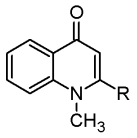
7



8

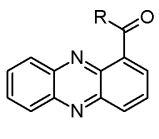


9

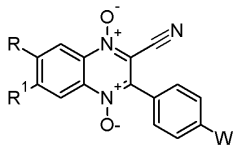


10

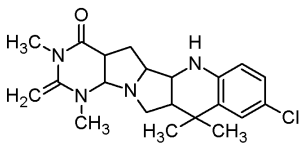
new compounds (**11**) have shown activity in a concentration range of 0.19-3.12 mg/L against tubercular resistant clinical isolates. This series of compounds were ineffective in inhibiting the growth of INH resistant strains. Compounds that had exocyclic groups with different lipophilic and electronic propertiesbut with a size similar to INH (such as phenylamide methyl group) in 4th position were found to be most active. Same group in 3rd position reduced activity to 100-fold. Phenazine derivatives having electron-withdrawing groups in 2nd and 3rd position have similar biological activity. The arylic moiety was found to be an important pharmacophoric feature for phenazine carboxamide anti-TB compounds. The mechanism of action of phenazine derivatives is still unknown and hypothesized that it could act as a cellular superoxide bismutase inhibitor. Inhibition of DNA dependent RNA polymerase is also suggested similar to Lomofungin (1-carbomethoxy-5-formyl-4,6,8-trihydroxyphenazine).[20] Quinoxaline derivatives have shown broad spectrum of biological activities. Quinoxaline-*N*-oxide derivatives are known as *M. tuberculosis* bioreductor agents. Compounds missing *N*-oxide groups have led to the loss of anti-TB activity. Over 500 derivatives of quinoxaline (**12**) were studied and it clearly demonstrated the importance of this group for developing a new class of anti-TB compounds. The quinoxaline compounds have activity on non-replicating bacteria, which could lead to shorter anti-TB activity.[21] A new derivative of quinolone denominated ER-2 (**13**) reported to inhibit gyrase supercoiling in *M. tuberculosis* similar to Ciprofloxacin with a MIC_{90} of 0.5μg/mL.[22]



11



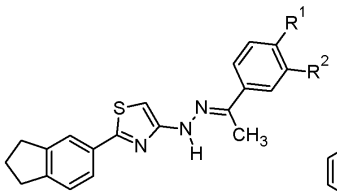
12



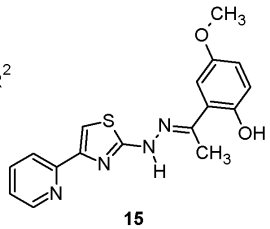
13

4. Hydrazides/hydrazones derivatives

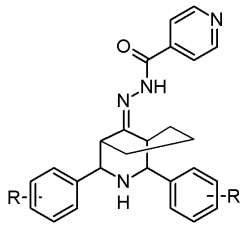
Hydrazide/hydrazone compounds have been considered for new anti-TB drug design. An example is Diflunisal, which has dual activity, antimicrobial and anti-inflammatory. A series of thiazolyl-hydrazone derivatives (**14**) were reported to have anti-TB activity and was influenced by the substitutions on the phenyl ring.[23] Another series of thiazolyl-hydrazine compound was reported with potential anti-TB activity. Compound (**15**) with pyridyl moiety was found to have IC_{50} of 6.22 μg/mL and CC_{50}> 40 μg/m.[24] A series of hydrozones of INH was also reported with potential anti-TB activity (**16**).[25] A new class of compounds designed through hybrid approach, incorporating the chemical features of E-cynamic acid and guanyl hydrazones has also been reported for their anti-TB activity. The electronic and steric features play an important role in determining the activity of this class of drugs on *M. tuberculosis* (**17**).[26]



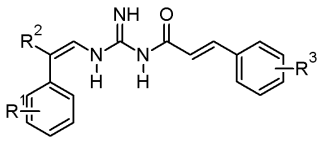
14



15



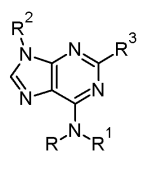
16



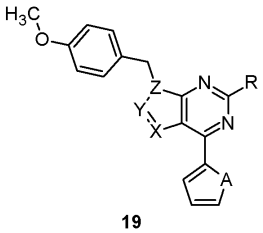
17

5. Nitrogen heterocyclic derivatives

Purines are an important scaffold in the design of anti-TB drugs. In these compounds (**18**), activity depends on the substituents present in C-2, C-6 and N-9 of the purine ring.[27] In 6,9-disubtituted purine derivatives, activity increases substantially when a C-l atom is presented in the 2-position. Purine derivatives with thienyl substituents exhibited better activity in non-replicating bacteria, although in these compounds a C-l atom in 2-position is not beneficial for activity. The purine N-9 is important for activity, in the case of purine C-8, an atom can be exchanged without losing activity and a change in purine N-7 results in a loss of activity, although there are 7-deazapurines derivatives (**19**) that could be compared with RIF.[28]



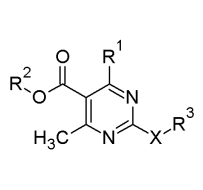
18



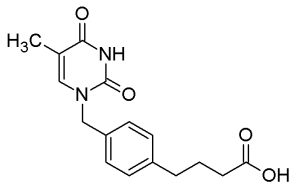
19

As pyrimidines have potential therapeutic applications as anti-TB agents, design of pyrimidine derivatives is a possible option (**20**). The nature of substituent at 2nd position can modulate cytotoxic activity.[29] The thymidine monophosphate kinase of *M. tuberculosis* (TMPKmt) is a prominent target for the development of anti-TB drugs. TMPK is the last specific enzyme for dNTP synthesis and is a key enzyme in *M. tuberculosis* metabolism. This enzyme is different from human enzyme analogs (22% homology). TMPK inhibitors have

been developed with single or multiple chemical modifications of the pyrimidine moiety and thymidylate sugar. In particular, benzyl-thymine derivatives have been remarkable TMPK inhibitors, which has led to the proposal of new modifications such as: chain length in *para*-position on the benzyl ring, unsaturation of the alkyl chain, functionalization of the chain group and substitution at 5th position of the core base. This has led to the identification of more selective compounds on TMKP that correspond to benzyl-pyrimidines substituted by a chain length of 4 carbon atoms and a terminal carboxylic acid function. Docking of molecule (**21**) on TMPKmt showed that the hydrogen of the thymine and acid group can interact with Arg95.[30]

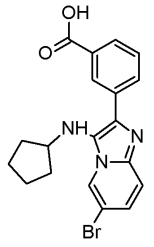


20

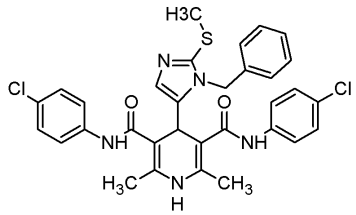


21

Pyridine derivatives have also been illustrated as anti-TB agents, compound (**22**), presenting inhibitory activity with an IC_{50} value of 0.38 μM, being its possible mechanism of action through glutamine synthetase inhibition. This would be the first inhibitor compound not derived from amino acids against the proposed target.[31] Another series of pyridine derivatives were developed, as the case of compound (**23**), a potent anti-TB agent with activity similar to RIF. The results showed that an imidazole group as a substituent is equivalent to a nitro phenyl group, which has been reported in anti-TB agents derived from 1,4-dihydropyridinecarboxamides.[32]

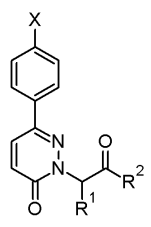


22



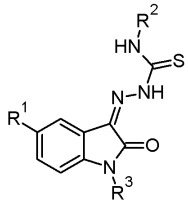
23

Another important heterocyclic for the design of anti-TB compounds is a pyridazine moiety. In these compounds a relationship between Br, Cl and CH_3 substituents, respectively, with Br and vinyl has been found with a favorable anti-TB activity. In these compounds there is an influence of the substituents X in *para*-position on the aromatic ring, where the activity is increased in the following order: CH_3<Cl< Br with the activity being affected by the R_1 substituents, where the most active compounds have a CH_3 group (**24**).[33]

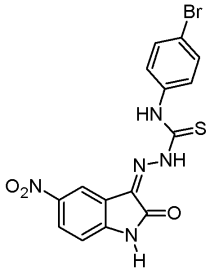


24

Thethiosemicarbazone derivatives of isatin can be used in TB therapy and prophylaxis. The 1H-2-thiosemicarbazoneindolinone derivatives indicated that halogenation of R_1, elongation of the alkyl chain in R_2, substitutions of the alkyl chain in R_2 with cyclohexyl or phenyl, and the presence of a substituent in R_3, are more efficient for increasing anti-TB activity, while R_1 substitutions with a nitro group produce the most active compounds. The presence of a morpholine ring in Schiff bases substituted in R_1 with a nitro group has a significant impact on anti-TB activity. The results indicated that the elongation of the alkyl chain increases activity. This enhanced activity is related to lipophilicity properties. Also, replacement of the alkyl chain in R_2 and phenyl unsubstituted cyclohexyl has led to more active compounds (**25**). The absence of substitutions at N_1 on the indole ring and increased lipophilicity appear to be responsible for high activity against *M. tuberculosis*.[34] The thiosemicarbazone-derived compounds have exhibited important anti-TB activity with an IC_{50} value of 2.59 μM/mL and it is compound (**26**).[35]

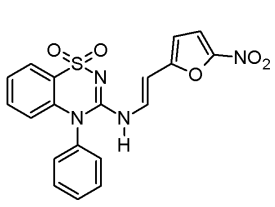


25

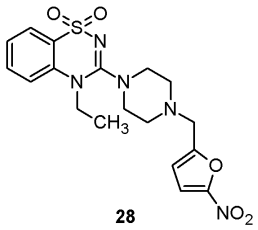


26

Other moieties used in the design of anti-TB drugs are phenazine and benzothidiazine, particularly benzothidiazine 1,1-dioxide constituents are important anti-TB agents (**27**). These compounds indicate that the furan and thiophene group linked to benzothidiazine through a methylene bridge exhibited good anti-TB activity. The conjugated thiophene derivative showed moderate activity and is enhanced when it presents a nitrofuran group. The elimination of the methylene group with a carbonyl group leads to a loss of activity. The piperazine-benzothidiazine with methylene linkage (**28**) is an attractive moiety for the design of anti-TB agents.[36]



27

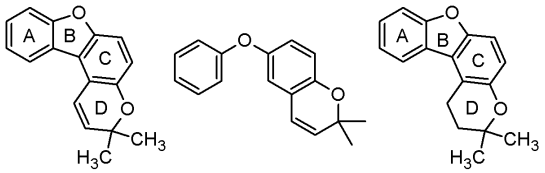


28

6. Other non-nitrogen heterocyclic derivatives

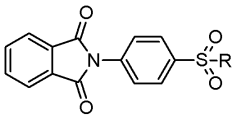
The hybrid compound has been used for the design of anti-TB agents such as compound (**29**), formed from dibenzofuran and 2,2- dimethyl pyran subunits. The modifications of benzofuro benzopyran have showed less active compounds such as compound (**30**), where the furan B ring is replaced by an ether linker, a carbonyl group, a hydroxy methylene or a methylene group. The modifications such as acylation and bromination in 5-position on the C ring have produced inactive compounds. Other derivatives of compound (**29**), like substitutions with a hydroxy, methoxy, or halogen group on benzofuro benzopyran increases anti-TB activity. The hydroxy compounds with good activity

also showed cytotoxic activity on VERO cells. Halogenated compounds with a Cl or Br atom in 8, 9 and 11-position, exhibit improved potency than compound (**29)**. The potency was significantly decreased when the A ring was substituted by an electron withdrawing group. The electron donating group substitutions such as hydroxy or methoxy showed significant increase activity (**31**). All these compounds showed a possible mechanism of action of interaction with lipid biosynthesis of the *M. tuberculosis* cell wall and act as an epoxy-mycolate synthesis inhibitor.[37]



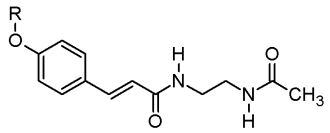
29 **30** **31**

Other compounds with phthalimide moiety have described as biophoro to design new drugs with different biological activities. The hybridization of both phthalimide (thalidomide) and sulfonamide (dapsone) moiety leads to compounds with antileprotic activity. The design of new compounds with anti-TB activity is interesting. A series of derivatives showed that if the pyrimidine ring is substituted in any position or changed by an isosteric, this decreases anti-TB activity. Amino group substitutions by phthalimide ring also lead to a decrease anti-TB activity (**32**). Modifications in the pyridine ring decrease anti-TB activity. The phthalimide group by molecular hybridization did not produce compounds with activity similar to INH; however, it allowed for compounds with MIC values similar to PZA.[38]



32

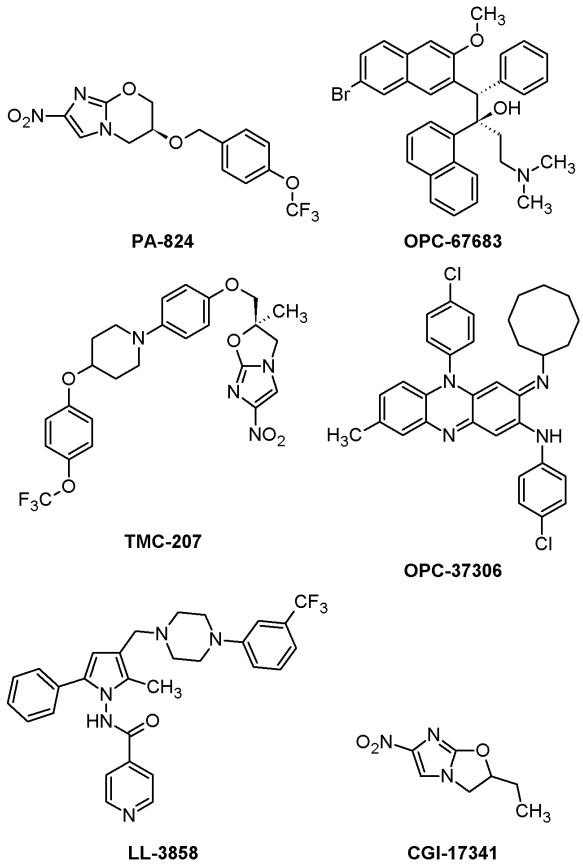
The compounds that act as inhibitors of the FAS-II system, diphenyl ether that interact with enzyme-cofactor binary complex, new compounds such as indoles, benzofuran and cinnamic acid derivatives have been reported. Development of cinnamic acid derivatives would focus on more specific FAS-II inhibitors. A series of compounds (**33**) was determined that addition of an alkyl chain increases anti-TB activity. A compound with geranyl substitution at R position was the most active substance with an MIC of 0.1μg/mL.[39] The amide derivatives of fatty acids have anti-TB activity. These compounds are designed to penetrate bacterial cells, which can be useful for the mechanism of INH resistance, this can be due to factors such as mutations in unknown genes, decreased permeability, or increased efflux.[40]



33

7. Drugs in clinical trials

The bicyclic nitroimidazofurane derivatives have anti-TB activity, such as CGI-17341, this compound is mutagenic. This has led to the development of PA-824. Its mechanism of action is to inhibit *M. tuberculosis* cell wall lipids and protein synthesis. It also inhibits non-replicating bacteria. The derived oxazoles as anti-TB compounds led to the development of OPC-67683, which has excellent activity in sensitive and resistant *M. tuberculosis* strains. Its mechanism of action involves inhibition of the synthesis of keto-mycolic, and methoxy-mycolic acid, although it can exist another possible mechanism of action or interaction with another drug target in *M. tuberculosis.* The OPC-67683 also acts as a prodrug, since *M. tuberculosis* metabolizes it and produces desnitro-imidazooxazole metabolite as a product. TMC207 is a quinoline derivative with potent anti-TB activity in susceptible, DR and XDR strains. Its mechanism of action involves inhibition of ATP synthase that binds the *M. tuberculosis* membrane and there is a synergistic effect between TMC207 and PZA. Other very promising anti-TB compounds are LL-3858 and OPC-37306.[41-43]



PA-824 **OPC-67683**

TMC-207 **OPC-37306**

LL-3858 **CGI-17341**

8. Conclusion

Despite the availability of chemotherapy and vaccine (BCG), TB remains the leading infectious disease worldwide.. Structure-based drug design strategies provided a platform to identify newer and potential candidates as anti-TB agents.[44, 45] Through high-throughput virtual screening of existing database of chemical compounds, newer scaffold with novel anti-TB activity are being identified and are under investigation.

References

1. Asif, M., Study of clinically used and recently developed antimycobacterial agents. *Orient Pharm Exp Med* 2012, 12, 15-34.
2. Zhang, Y.; Post-Martens, K.; Denkin, S., New drug candidates and therapeutic targets for tuberculosis therapy. *Drug Discov Today* 2006, 11, 21-7.

3. Hasan, S.; Daugelat, S.; Rao, P. S.; Schreiber, M., Prioritizing genomic drug targets in pathogens: application to *Mycobacterium tuberculosis*. *PLoS Comput Biol* 2006, 2, e61.
4. Zhang, Y., Persistent and dormant tubercle bacilli and latent tuberculosis. *Front Biosci* 2004, 9, 1136-56.
5. Dye, C., Global epidemiology of tuberculosis. *Lancet* 2006, 367, 938-40.
6. Asif, M., Recent Efforts for the Development of Antitubercular Drug Containing Diazine Ring. *Med Chem* 2012, 2, 151-67.
7. Blumberg, H.; Burman, W.; Chaisson, R.; Daley, C.; Etkind, S.; Friedman, L.; Fujiwara, P.; Grzemska, M.; Hopewell, P.; Iseman, M., American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Resp Crit Care Med* 2003, 167, 603.
8. Asif, M., Mini review on Ethmabutol and its some analogues as antitubercular agents. *Elixir Pharm* 2012, 53, 11774-8.
9. Asif, M., Study of currently used antimycobacterials, their analogoues and recently developed agents. *Indian Drugs* 2012, 49, 5-19.
10. Zhang, Y.; Amzel, L., Tuberculosis drug targets. *Curr Drug Targets* 2002, 3, 131-54.
11. Asif, M.; Siddiqui, A. A.; Husain, A., Quinolone derivatives as antitubercular drugs. *Med Chem Res* 2013, 22, 1029-42.
12. Asif, M., A review on potent antitubercular agent isoniazid and its Analogues. *Int J Pharm Chem* 2013, 2, 110-20.
13. Eswaran, S.; Adhikari, A. V.; Ajay Kumar, R., New 1, 3-oxazolo [4, 5-*c*] quinoline derivatives: Synthesis and evaluation of antibacterial and antituberculosis properties. *Eur J Med Chem* 2010, 45, 957-66.
14. Eswaran, S.; Adhikari, A. V.; Chowdhury, I. H.; Pal, N. K.; Thomas, K., New quinoline derivatives: Synthesis and investigation of antibacterial and antituberculosis properties. *Eur J Med Chem* 2010, 45, 3374-83.
15. Gonçalves, R. S.; Kaiser, C. R.; Lourenco, M.; de Souza, M. V.; Wardell, J. L.; Wardell, S. M.; da Silva, A. D., Synthesis and antitubercular activity of new mefloquine-oxazolidine derivatives. *Eur J Med Chem* 2010, 45, 6095-100.
16. Mao, J.; Yuan, H.; Wang, Y.; Wan, B.; Pak, D.; He, R.; Franzblau, S. G., Synthesis and antituberculosis activity of novel mefloquine-isoxazole carboxylic esters as prodrugs. *Bioorg Med Chem Lett* 2010, 20, 1263-8.
17. Kini, S. G.; Bhat, A. R.; Bryant, B.; Williamson, J. S.; Dayan, F. E., Synthesis, antitubercular activity and docking study of novel cyclic azole substituted diphenyl ether derivatives. *Eur J Med Chem* 2009, 44, 492-500.
18. Yang, C.-L.; Tseng, C.-H.; Chen, Y.-L.; Lu, C.-M.; Kao, C.-L.; Wu, M.-H.; Tzeng, C.-C., Identification of benzofuro [2, 3- *b*] quinoline derivatives as a new class of antituberculosis agents. *Eur J Med Chem* 2010, 45, 602-7.
19. Wube, A. A.; Hüfner, A.; Thomaschitz, C.; Blunder, M.; Kollroser, M.; Bauer, R.; Bucar, F., Design, synthesis and antimycobacterial activities of 1-methyl-2-alkenyl-4 (1 *H*)-quinolones. *Bioorg Med Chem* 2011, 19, 567-79.
20. De Logu, A.; Palchykovska, L. H.; Kostina, V. H.; Sanna, A.; Meleddu, R.; Chisu, L.; Alexeeva, I. V.; Shved, A. D., Novel *N*-aryl-and *N*-heteryl phenazine-1-carboxamides as potential agents for the treatment of infections sustained by drug-resistant and multidrug-resistant *Mycobacterium tuberculosis*. *Int J Antimicrob Ag* 2009, 33, 223-9.
21. Vicente, E.; Pérez-Silanes, S.; Lima, L. M.; Ancizu, S.; Burguete, A.; Solano, B.; Villar, R.; Aldana, I.; Monge, A., Selective activity against *Mycobacterium tuberculosis* of new quinoxaline 1, 4-di- *N*-oxides. *Bioorg Med Chem* 2009, 17, 385-9.
22. Rao, S. S.; Raghunathan, R.; Ekambaram, R.; Raghunathan, M., In vitro activities of the newly synthesised ER-2 against clinical isolates of Mycobacterium tuberculosis susceptible or resistant to antituberculosis drugs. *Int J Antimicrob Ag* 2009, 34, 451-3.
23. Turan-Zitouni, G.; Özdemir, A.; Asim Kaplancikli, Z.; Benkli, K.; Chevallet, P.; Akalin, G., Synthesis and antituberculosis activity of new thiazolylhydrazone derivatives. *Eur J Med Chem* 2008, 43, 981-5.
24. Turan-Zitouni, G.; Kaplancıklı, Z. A.; Özdemir, A., Synthesis and antituberculosis activity of some *N*-pyridyl- *N*′-thiazolylhydrazine derivatives. *Eur J Med Chem* 2010, 45, 2085-8.
25. Sankar, C.; Pandiarajan, K., Synthesis and anti-tubercular and antimicrobial activities of some 2r, 4 *c*-diaryl-3-azabicyclo [3.3. 1] nonan-9-one *N*-isonicotinoylhydrazone derivatives. *Eur J Med Chem* 2010, 45, 5480-5.
26. Bairwa, R.; Kakwani, M.; Tawari, N. R.; Lalchandani, J.; Ray, M. K.; Rajan, M. G. R.; Degani, M. S., Novel molecular hybrids of cinnamic acids and guanylhydrazones as potential antitubercular agents. *Bioorg Med Chem Lett* 2010, 20, 1623-5.
27. Correia, C.; Carvalho, M. A.; Proença, M. F., Synthesis and in vitro activity of 6-amino-2, 9-diarylpurines for *Mycobacterium tuberculosis*. *Tetrahedron* 2009, 65, 6903-11.
28. Khoje, A. D.; Kulendrn, A.; Charnock, C.; Wan, B.; Franzblau, S.; Gundersen, L.-L., Synthesis of non-purine analogs of 6-aryl-9-benzylpurines, and their antimycobacterial activities. Compounds modified in the imidazole ring. *Bioorg Med Chem* 2010, 18, 7274-82.
29. Singh, K.; Singh, K.; Wan, B.; Franzblau, S.; Chibale, K.; Balzarini, J., Facile transformation of Biginelli pyrimidin-2(1H)-ones to pyrimidines. In vitro evaluation as inhibitors of *Mycobacterium tuberculosis* and modulators of cytostatic activity. *Eur J Med Chem* 2011, 46, 2290-4.
30. Gasse, C.; Douguet, D.; Huteau, V.; Marchal, G.; Munier-Lehmann, H.; Pochet, S., Substituted benzyl-pyrimidines targeting thymidine monophosphate kinase of *Mycobacterium tuberculosis*: Synthesis and in vitro anti-mycobacterial activity. *Bioorg Med Chem* 2008, 16, 6075-85.
31. Odell, L. R.; Nilsson, M. T.; Gising, J.; Lagerlund, O.; Muthas, D.; Nordqvist, A.; Karlén, A.; Larhed, M., Functionalized 3-amino-imidazo [1, 2-*a*] pyridines: A novel class of drug-like *Mycobacterium tuberculosis* glutamine synthetase inhibitors. *Bioorg Med Chem Lett* 2009, 19, 4790-3.
32. Fassihi, A.; Azadpour, Z.; Delbari, N.; Saghaie, L.; Memarian, H. R.; Sabet, R.; Alborzi, A.; Miri, R.; Pourabbas, B.; Mardaneh, J.; Mousavi, P.; Moeinifard, B.; Sadeghi-aliabadi, H., Synthesis and antitubercular activity of novel 4-substituted imidazolyl-2,6-dimethyl-N3,N5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides. *Eur J Med Chem* 2009, 44, 3253-8.
33. Mantu, D.; Cătălina Luca, M.; Moldoveanu, C.; Zbancioc, G.; Mangalagiu, I. I., Synthesis and antituberculosis activity of some new pyridazine derivatives. Part II. *Eur J Med Chem* 2010, 45, 5164-8.
34. Güzel, Ö.; Karalı, N.; Salman, A., Synthesis and antituberculosis activity of 5-methyl/trifluoromethoxy-1H-indole-2,3-dione 3-thiosemicarbazone derivatives. *Bioorg Med Chem* 2008, 16, 8976-87.
35. Karalı, N.; Gürsoy, A.; Kandemirli, F.; Shvets, N.; Kaynak, F. B.; Özbey, S.; Kovalishyn, V.; Dimoglo, A., Synthesis and structure–antituberculosis activity relationship of 1H-indole-2,3-dione derivatives. *Bioorg Med Chem* 2007, 15, 5888-904.

36. Kamal, A.; Shetti, R. V. C. R. N. C.; Azeeza, S.; Ahmed, S. K.; Swapna, P.; Reddy, A. M.; Khan, I. A.; Sharma, S.; Abdullah, S. T., Anti-tubercular agents. Part 5: Synthesis and biological evaluation of benzothiadiazine 1,1-dioxide based congeners. *Eur J Med Chem* 2010, 45, 4545-53.
37. Termentzi, A.; Khouri, I.; Gaslonde, T.; Prado, S.; Saint-Joanis, B.; Bardou, F.; Amanatiadou, E. P.; Vizirianakis, I. S.; Kordulakova, J.; Jackson, M.; Brosch, R.; Janin, Y. L.; Daffé, M.; Tillequin, F.; Michel, S., Synthesis, biological activity, and evaluation of the mode of action of novel antitubercular benzofurobenzopyrans substituted on A ring. *Eur J Med Chem* 2010, 45, 5833-47.
38. Santos, J. L.; Yamasaki, P. R.; Chin, C. M.; Takashi, C. H.; Pavan, F. R.; Leite, C. Q. F., Synthesis and in vitro anti *Mycobacterium tuberculosis* activity of a series of phthalimide derivatives. *Bioorg Med Chem* 2009, 17, 3795-9.
39. Yoya, G. K.; Bedos-Belval, F.; Constant, P.; Duran, H.; Daffé, M.; Baltas, M., Synthesis and evaluation of a novel series of pseudo-cinnamic derivatives as antituberculosis agents. *Bioorg Med Chem Lett* 2009, 19, 341-3.
40. D'Oca, C. D. R. M.; Coelho, T.; Marinho, T. G.; Hack, C. R. L.; da Costa Duarte, R.; da Silva, P. A.; D'Oca, M. G. M., Synthesis and antituberculosis activity of new fatty acid amides. *Bioorg Med Chem Lett* 2010, 20, 5255-7.
41. Palomino, J. C.; Ramos, D. F.; da Silva, P. A., New anti-tuberculosis drugs: strategies, sources and new molecules. *Curr Med Chem* 2009, 16, 1898-904.
42. Rivers, E. C.; Mancera, R. L., New anti-tuberculosis drugs in clinical trials with novel mechanisms of action. *Drug Discov Today* 2008, 13, 1090-8.
43. Shi, R.; Sugawara, I., Development of new anti-tuberculosis drug candidates. *Tohoku J Exp Med* 2010, 221, 97-106.
44. Asif, M., A review of antimycobacterial drugs in development. *Mini Rev Med Chem* 2012, 12, 1404-18.
45. Janin, Y. L., Antituberculosis drugs: ten years of research. *Bioorg Med Chem* 2007, 15, 2479-513.